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Comparative Study of Encainide and Disopyramide in Chronic Ventricular Arrhythmias: A Double-Blind Placebo-Controlled Crossover Study

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Ten patients suffering from chronic premature ventricular complexes (>60/h) were treated orally in a double-blind crossover study with encainide (50 mg three times a day) and disopyramide (200 mg three times a day), with five 7 day study periods: survey, placebo, encainide or disopyramide, washout placebo and disopyramide or encainide. At the end of each 7 day period, a 12 lead electrocardiogram, a 48 hour ambulatory electrocardiogram and a treadmill exercise test were performed. Blood levels of encainide and its metabolites and of disopyramide were measured at the end of each treatment (steady state). Drug efficacy was assessed by: 1) more than 80% reduction in the number of premature ventricular complexes per 24 hours, and 2) absence of ventricular tachycardia.

Encainide was effective in four patients (complete suppression of premature ventricular complexes) and ineffective in five. One patient who showed a 92% reduction in the number of premature ventricular complexes developed sustained ventricular tachycardia after 24 hours of treatment. Disopyramide was effective in three patients (>80% reduction in the number of premature ventricular complexes) and ineffective in seven patients. With encainide, the percent increase in PR, QRS and QT interval duration was, respectively: 32.7 ($p < 0.001$), 30.8 ($p < 0.001$) and 10.6% ($p < 0.01$). With disopyramide this increase was not significant. Despite the variability of drug blood levels, a relation between blood levels and suppression of premature ventricular complexes on the 48 hour ambulatory electrocardiogram was found with encainide, but not with disopyramide. The side effects observed for encainide were visual disturbances and headache; for disopyramide, they were headache, dryness of mouth and dysuria.

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Patients with chronic premature ventricular complexes constitute an ideal study group for the assessment of new antiarrhythmic agents because such patients can tolerate periods of lack of treatment and placebo medication. Encainide, a benzanilide derivative, has proved to be highly effective in suppressing premature ventricular complexes and refractory recurrent ventricular tachycardia (1,2). It is classified as a type IC antiarrhythmic drug. Substantial increases in PR and QRS intervals occur during long-term encainide therapy in a manner related to dose and plasma concentration, and few hemodynamic side effects are noted (2). In a controlled trial in patients with premature ventricular complexes, encainide was shown to be more effective than quinidine (3).

Disopyramide phosphate, which also demonstrates type I antiarrhythmic action, is widely used in Europe for treatment of ventricular arrhythmias (4–6). Its pharmacologic profile is similar to that of quinidine and procainamide and it has been shown to have negative inotropic activity after both intravenous and oral administration (7).

In this study we compared the antiarrhythmic efficacy and safety of oral preparations of encainide and disopyramide in patients with chronic premature ventricular complexes. To accomplish this, a double-blind crossover study design was utilized.

Methods

Patients (Table 1). Ten patients (five men and five women) aged 16 to 69 years entered the study. Each patient

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Table 1. Clinical Characteristics of 10 Patients at Inclusion in the Study

Case	Age (yr) & Sex	Weight (kg)	Arrhythmia	Underlying Heart Disease	Other Medical Conditions	Concurrent Medications
1	56M	59	PVC	Myocardial infarction + angina pectoris	Hiatal hernia; acrocyanosis	Acenocoumarol
2	40F	64	PVC + nonsustained VT	Angina pectoris + hypertension	None	Altizide + spironolactone; lorazépam
3	28M	81	PVC	None	None	None
4	57M	78	PVC + PAC	Alcohol-associated cardiomyopathy; mitral regurgitation	Arthrosis	Furosemide, potassium
5	16F	57	PVC + sustained VT	Arrhythmogenic dysplasia	None	None
6	19F	50	PVC	None	None	None
7	31M	67	PVC	None	None	None
8	32F	49	PVC	None	None	None
9	53F	50	PVC + PAC	None	None	None
10	69M	79	PVC	Myocardial infarction	None	None

F = female; M = male; PAC = premature atrial complexes; PVC = premature ventricular complexes; VT = ventricular tachycardia.

had more than 60 premature ventricular complexes/h during an initial control study utilizing a 48 hour ambulatory electrocardiogram. Patients with a recent myocardial infarction, unstable angina, blood pressure above 180/120 or lower than 90/60 mm Hg, uncontrolled congestive heart failure, significant intracardiac conduction defect, atrioventricular block, significant hepatic or renal impairment, QRS interval greater than 0.12 second or PR interval greater than 0.3 second, glaucoma, myasthenia gravis or symptomatic prostatic hypertrophy were excluded from the study, as were pregnant or nursing women. Informed consent was obtained from each patient.

Trial design. A complete history and physical examination, 12 lead electrocardiogram, routine hematologic and chemical tests and urinalysis were performed at the initiation of the study. All previous antiarrthythmic agents were discontinued, and a baseline 48 hour ambulatory electrocardiogram was recorded after five half-lives of the previously administered drug had elapsed. Eligible subjects were randomly assigned to receive doses of disopyramide (200 mg every 8 hours) or encainide (50 mg every 8 hours) for 1 week.

After a 1 week period in which placebo was administered every 8 hours, a 48 hour ambulatory electrocardiogram was recorded to confirm an average rate of premature ventricular complexes greater than 60/h in all patients. Qualifying patients then received either encainide or disopyramide for 1 week. At the end of this second week, a 48 hour ambulatory electrocardiogram was recorded. During the third week, all the patients were again given placebo, after which a 48 hour ambulatory electrocardiogram was again obtained. During the fourth week, patients received the alternative drug regimen, and a 48 hour ambulatory electrocardiogram was again obtained at the end of this period. A 12 lead electrocardiogram, blood pressure and pulse rate were measured at each visit.

A symptom-limited exercise test was performed on a motor-driven treadmill using the Bruce protocol under conditions of maximal safety at the end of each week. The period of exercise was analyzed separately on the ambulatory electrocardiogram. Analysis focused on the frequency of premature ventricular complexes and runs during exercise in comparison with their prevalence during the remainder of the 24 hour electrocardiogram.

Patient compliance was confirmed by capsule count at each visit. Randomization of initial treatment, alternate crossover treatment and placebo were prepared through coding and identical packaging of active drugs and placebo. All patient conditions during therapy were reported.

Drug assessment. Patients were considered to be responders if the average frequency of premature ventricular complexes was suppressed by 80% of the baseline value. This level was chosen to reduce the influence of spontaneous variability. Episodes of ventricular tachycardia (defined as three or more consecutive premature ventricular complexes) were also recorded in patients during baseline measurements and during each treatment sequence. Absence of total suppression of ventricular tachycardia was considered to be a drug failure. Ventricular tachycardia was defined as sustained if it lasted 30 seconds or longer. Nonsustained ventricular tachycardia was defined as any event of 10 sequential complexes that lasted less than 30 seconds.

Plasma concentration determination. Blood samples (10 ml) were collected by direct venipuncture before the morning intake, and 90 minutes after the intake on day 7 of weeks 2 and 4 (active drug weeks). After centrifugation, the plasma samples were stored at −20°C until assayed. Analysis was performed by high performance liquid chromatography, which detects both encainide and two of its major metabolites, 0-demethyl encainide (ODE) and 3-methoxy-0-demethyl encainide (MODE). Disopyramide was assayed using liquid chromatography after extraction from plasma.

Statistical analysis. Grouped data were compared using the paired two-tailed Students *t* test. A value of $p < 0.05$ was considered to be statistically significant.

Results

Suppression of ventricular arrhythmias. All 10 patients completed the study, and all the available data were included in the analysis. The number of premature ventricular complexes per hour for each of the patients over the course of the five phases of the study are presented in Figures 1 and 2. The mean percent suppression of premature ventricular complexes was 61.7% after encainide therapy compared with 44.1% after disopyramide. The decrease in ventricular ectopic activity compared with baseline was statistically significant for both encainide ($p < 0.01$) and disopyramide therapy ($p < 0.05$). No significant differences were noted between the baseline values and each of the two placebo measurements preceding encainide and disopyramide therapy.

During the encainide phase, 4 of the 10 patients showed complete suppression of premature ventricular complexes (defined as <10 premature ventricular complexes per 24 hours), and 5 patients had less than 80% reduction in premature ventricular complexes with or without complete suppression of episodes of ventricular tachycardia. One patient developed sustained ventricular tachycardia after 26 hours of treatment, despite a 92% suppression of premature ventricular complexes (Fig. 3).

During the disopyramide phase, 3 of the 10 patients exhibited greater than 80% suppression of premature ventricular complexes, 6 patients had less than an 80% reduction and in 1 patient, despite an 80% reduction, runs of ventricular tachycardia documented during baseline ambulatory monitoring were not suppressed (Fig. 3).

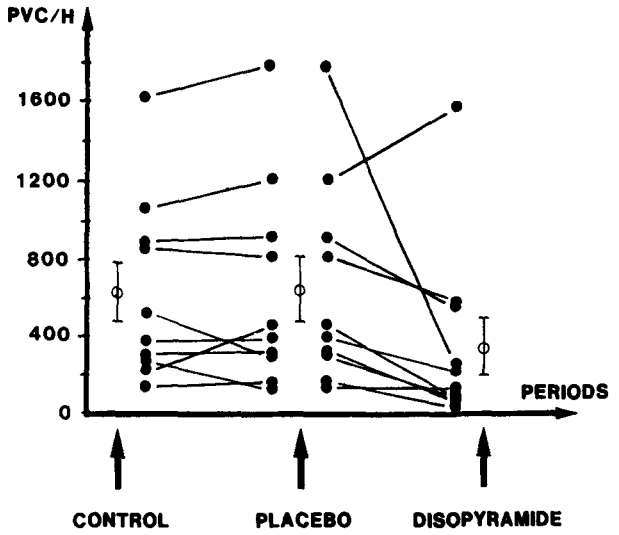

Figure 2. Effects of disopyramide on premature ventricular complex (PVC) frequency per hour (H) in 10 patients. Symbols as in Figure 1.

Figure 1. Effects of encainide on premature ventricular complex (PVC) frequency per hour (H) in 10 patients. **Open circles** indicate mean values; **vertical bars** show the standard error of the mean.

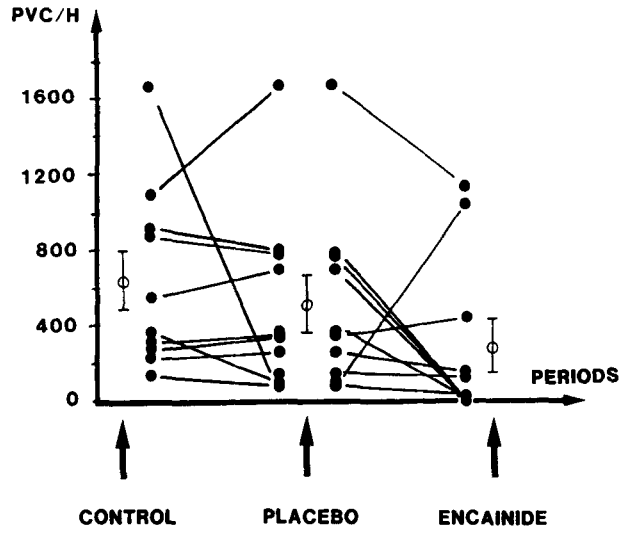

Figure 3. Percent variations in premature ventricular complex (PVC) frequency with encainide and disopyramide. Efficacy is assessed as an 80% decrease in the number of premature ventricular complexes in comparison with that during the control period (0).

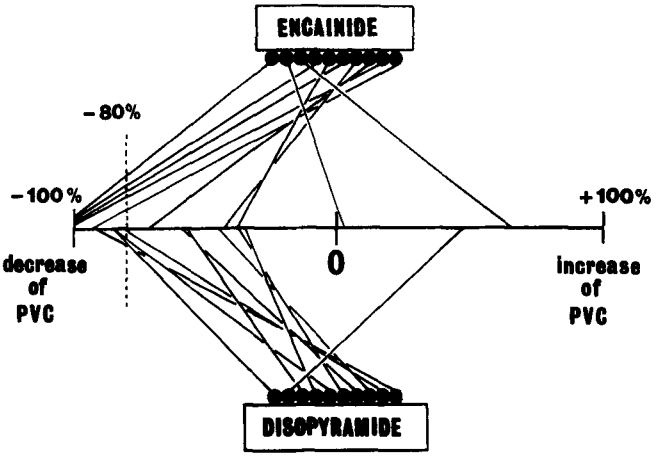

Table 2. Variations in Electrocardiographic Interval Values During Encainide and Disopyramide Therapy in Comparison With Values During the Control Period

	Electrocardiographic Interval (ms)		
	PR	QRS	QTc
Control	156 ± 23	86 ± 11	423 ± 22
Encainide	207 ± 34	112 ± 18	467 ± 46
△%	32.7*	30.8*	10.6†
Disopyramide	162 ± 26	94 ± 15	439 ± 28
△%	3.8‡	9.3‡	4.0‡

Compared with control period values, *$p < 0.001$; †$p < 0.01$; ‡p = NS. Data are reported as mean values ± SD. △% = percent variation compared with control values.

Vital signs. No clinically significant changes in blood pressure and heart rate were noted for either drug during the course of the study compared with baseline.

Electrocardiographic interval changes (Table 2). During the course of the study, encainide affected certain electrocardiographic intervals. There was a mean increase in the PR interval of 32.7% ($p < 0.001$), a 30.8% increase in QRS duration ($p < 0.001$) and a 10.6% increase in the QTc interval ($p < 0.01$). No significant changes were found during the disopyramide phase. The QTc intervals were increased up to 0.50 second in two patients (the baseline values were 0.44 and 0.45 second, respectively) and up to 0.54 second in one patient (baseline value 0.43 second) after encainide administration.

Exercise testing (Table 3). The frequency of premature ventricular complexes and the occurrence of paired premature ventricular complexes and ventricular tachycardia during exercise and during 5 minutes of recovery were compared for the placebo, encainide and disopyramide treatment periods. During the placebo phase, 9 of the 10 patients exhibited premature ventricular complexes, the majority having more than 10 during exercise and recovery periods. After receiving encainide, only two patients manifested premature ventricular complexes, whereas after receiving disopyramide six patients continued to have premature ventricular complexes during exercise.

Drug concentrations. The mean (± SD) trough plasma concentrations of encainide, and its metabolites (ODE and MODE) were 19.6 ± 27.9, 138.7 ± 126.1 and 98.9 ± 35.6 ng/ml, respectively. Because the two metabolites are active, an estimate was made by assuming equipotency, and the antiarrhythmic activity was expressed as the sum of

Table 3. Exercise Treadmill Test: Frequency of Ventricular Arrhythmias During Placebo and Active Drug Treatment Sequences

	Placebo			Encainide			Disopyramide		
Case	PVC	Pairs	Runs	PVC	Pairs	Runs	PVC	Pairs	Runs
1	+b	0	0	0	0	0	0	0	0
2	+b	+	+	0	0	0	+a	+	0
3	+b	0	0	+b	0	0	+a	0	0
4	+a	0	0	0	0	0	+a	0	0
5	0	0	0	0	0	0	0	0	0
6	+b	0	0	0	0	0	+b	0	0
7	+b	0	0	0	0	0	0	0	0
8	+b	0	0	+b	0	0	+b	0	0
9	+a	0	0	0	0	0	0	0	0
10	+b	+	0	ND	ND	ND	+a	0	0

a = less than 10 premature ventricular complexes during exercise and during 5 minutes of recovery; b = more than 10 premature ventricular complexes during exercise and during 5 minutes of recovery; ND = not done; PVC = premature ventricular complexes; + = presence; 0 = absence.

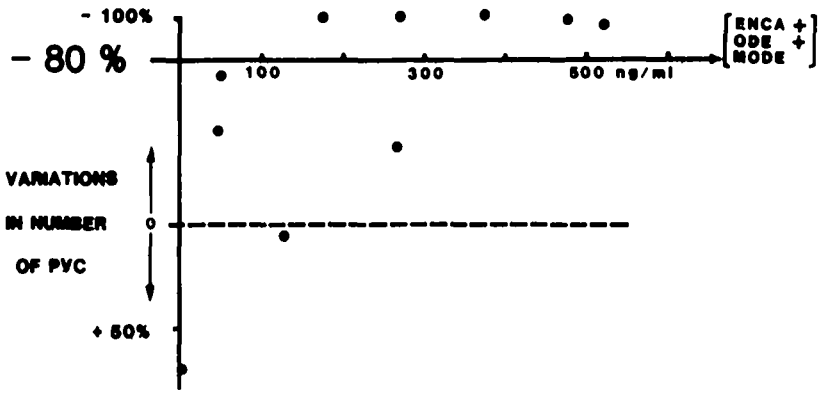

Figure 4. Relation between trough plasma levels of encainide and its metabolites (ODE, MODE) and the antiarrhythmic efficacy on day 7 of treatment in 10 patients. ENCA + ODE + MODE = the sum of plasma levels of encainide, 0-demethyl encainide and 3-methoxy-0-demethyl encainide. PVC = premature ventricular complexes.

encainide and two metabolites plasma concentrations. Except for one patient, the highest values were usually observed in patients who responded to therapy (Fig. 4). Importantly, the patient who failed to respond had no detectable plasma levels of encainide or either metabolite. Because normal concentrations were found 1 hour after a dose was administered in the clinic, and considering the long serum half-life of MODE, noncompliance seems likely. No relation could be established between plasma levels of disopyramide and antiarrhythmic effect (Fig. 5). The mean plasma concentration of disopyramide was 1.6 ± 0.8 μg/ml.

Side effects. During encainide therapy, three patients had mild headache, one patient had mild dizziness and one patient had visual disturbance. After 26 hours of encainide therapy, one patient developed sustained ventricular tachycardia with a wide QRS interval (240 ms) and a heart rate of 150 beats/min initiated by a couplet with a long interval (520 ms). Treatment was discontinued in this patient and cardioversion successfully terminated the ventricular tachycardia. The next day, the patient had ventricular tachycardia which was controlled by intravenous procainamide. This patient had a previous myocardial infarction, a large left ventricular aneurysm and a serum potassium level of 3.5 mEq/liter. It was difficult to assign a proarrhythmic role to encainide because of these factors plus the previous occurrence of several episodes of sustained ventricular tachycardia before encainide therapy. While taking disopyramide, one patient complained of dry mouth, one patient had a mild headache and one patient suffered from moderate dysuria which lessened after a 50% reduction of the dosage.

Discussion

Clinical efficacy. It is necessary to compare a new antiarrhythmic agent with widely used and marketed antiarrhythmic drugs. We chose a double-blind, randomized crossover protocol to compare encainide with disopyramide. Regarding the design of this study, several points are worthy of note. To exclude patients whose premature ventricular complexes were reduced spontaneously, patients were selected after two 24 hour ambulatory electrocardiograms that exhibited at least a mean of 60 premature ventricular complexes per hour. A 1 week placebo interval between the administration of the two antiarrhythmic drugs ensured complete washout of the effects of each drug. The 1 week period of treatment with encainide was justified by pharmacokinetic data. Kates et al. (8) have shown that quasi-steady state serum concentrations of the principal pharmacologically ac-

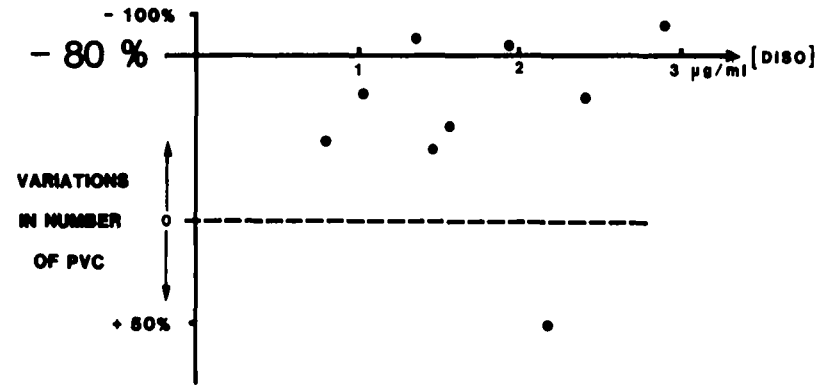

Figure 5. Relation between trough plasma levels of disopyramide (DISO) and the antiarrhythmic efficacy on day 7 of treatment in nine patients. (For technical reasons one datum is not present) PVC = premature ventricular complexes.

tive metabolites are found at 2 to 3 days in the case of ODE and at 1 week with MODE.

Our results suggest that both encainide and disopyramide were efficacious for treating chronic ventricular arrhythmia. Encainide was superior to disopyramide in suppression of premature ventricular complexes (4 of 10 patients with encainide versus 0 of 10 patients with disopyramide; $p < 0.001$). The mean percent suppression of premature ventricular complexes compared with baseline values was greater for encainide (61.7%) than for disopyramide (44.1%), but the difference was not statistically significant.

In a double-blind, randomized crossover study comparing encainide (200 mg/day) and quinidine (1,200 mg/day), Sami et al. (3) reported that encainide was more effective than quinidine in the treatment of ventricular ectopic activity. Consistent with our results, complete suppression of premature ventricular complexes was noted in 44% of their patients. In contrast, no patient demonstrated total suppression of premature ventricular complexes with quinidine.

Other studies have suggested that encainide is extremely effective in suppressing chronic ventricular arrhythmia, and the reported results (9) exceed the average suppression rate of other antiarrhythmic drugs. Complete suppression of premature ventricular complexes was rare with quinidine (10,11), procainamide (11), disopyramide (12), tocainide (13,14) and ethmozin (15,16), while flecainide (17,18) and lorcainide (19) exhibited degrees of suppression of ventricular ectopic activity comparable with those obtained with encainide. In addition, encainide was found an effective, well tolerated drug for the treatment of drug-refractory ventricular tachycardia (20). In our study, encainide significantly prolonged the PR, QRS and QTc intervals. These prolongations were seen as a manisfestation of the pharmacology of encainide and its metabolites.

Side effects. Encainide caused minor side effects, but discontinuation of therapy was not required except in one patient who had ventricular tachycardia. In this patient, encainide was suspected to initiate the tachycardia. The potential of all antiarrhythmic agents to provoke or aggravate ventricular arrhythmia is widely recognized. In a recent retrospective study, Velebit et al. (21) determined the frequency of aggravation of arrhythmia with nine antiarrhythmic drugs (quinidine, procainamide, disopyramide, propranolol, metoprolol, aprindine, mexiletine, tocainide and pindolol). The frequency for a specific drug ranged from 5.9 to 15.8%. According to Winkle et al. (20), the risk of encainide-induced ventricular tachycardia was 11% in 90 patients receiving the drug for recurrent sustained ventricular tachycardia or ventricular fibrillation, or both, and 2.2% in 47 patients receiving the drug for chronic complex ventricular ectopic activity.

A drug-induced arrhythmic aggravation is not yet predictable, although several risk factors (namely, the presence of ischemic heart disease, ventricular dysfunction, type of ventricular arrhythmia and lack of response to other antiarrhythmic agents) have been tentatively identified. Cohen et al. (22) showed that patients with ventricular tachycardia had a significantly larger aneurysm and a higher prevalence of septal akinesia or dyskinesia. Rochemaure et al. (23) also found that 28% of a group of 39 patients with a large aneurysm had ventricular tachycardia, whereas only 2% of a group of 48 patients with a small aneurysm developed ventricular tachycardia.

In agreement with these findings, our patient who had a possible encainide-induced ventricular tachycardia had a large aneurysm. Moreover, in this patient, a blood sample was drawn 2 hours before the episode of ventricular tachycardia and just before the last intake of the drug. ODE metabolite concentration was 308 ng/ml. Several studies have demonstrated that ODE and MODE metabolites account for some of encainide's toxicity and efficacy. In a recent report, Dawson et al. (24) showed that concentrations of ODE greater than 300 ng/ml can significantly lower the ventricular fibrillation threshold in an ischemic canine model. Nonetheless, higher serum concentrations of ODE are found in patients not exhibiting a drug-induced aggravation of arrhythmia. One could speculate that three factors contributed to the worsening of arrhythmia in our patient: ventricular aneurysm, hypokalemia and a high concentration of ODE. During disopyramide treatment, three of our patients complained of side effects that did not require withdrawal of the drug.

Conclusions. Encainide is a highly effective antiarrhythmic agent. It appears to be superior to disopyramide for complete suppression of premature ventricular complexes. Although encainide is a well tolerated drug, it may exacerbate cardiac arrhythmias in some patients.

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